REMARKS

Formalities

Claims 30, 32 and 33 were examined, and stand rejected. Claims 1-29, 31 and 34-35 have been canceled in a previous amendment.

Applicant respectfully requests reconsideration of the application in light of the arguments presented below.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 30, 32 and 33 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully traverses this rejection.

Claims 30, 32 and 33 are drawn to a transgenic mouse whose genome comprises a disruption in the melanocyte stimulating hormone receptor gene, specifically set forth in SEQ ID NO:19, which disruption results in a specific phenotype of hypoactivity (decreased activity).

In the rejection, the Examiner has argued that the specification does not provide an enabling disclosure for how to use the transgenic mouse as claimed. Essentially, the Examiner is rejecting the claims based on an alleged lack of utility, as a result of the transgenic mouse not exhibiting a useful phenotype. More particularly, the Examiner argues that the specification fails to provide specific teachings on how to use the claimed mouse with a phenotype of hypoactivity. The Examiner further suggests that the specification fails to teach a relationship between the disclosed phenotypes and a disease, presumably a human disease. Applicant respectfully disagrees with the Examiner's conclusions.

Applicant submits that knockout mice are well-established as a useful tool in the scientific community. One skilled in the art would easily recognize how to use the claimed transgenic mouse as, for example, a means of determining or characterizing the role or function of the melanocyte stimulating hormone receptor gene.

As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be

determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted as one of the premier models for determining gene function. Therefore, one skilled in the art would clearly know how to use a knockout mouse, such as the claimed mouse, in experiments designed to determine the function of the target gene. Countless means of using a knockout mouse for investigating the role or function of the disrupted gene exist and are well-known in the art. These include, but are not limited to, behavioral tests, expression analysis, histopathalogical analysis, reproductive or fertility tests, metabolic tests, and the like, and may or may not involve testing the effect of putative or known therapeutic agents on observed characteristics of the knockout mouse.

In addition, the commercial use and acceptance of knockout mice supports that a person skilled in the art would recognize how to use the claimed invention. Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. Multiple commercial entities, including three of the largest pharmaceutical companies in the world, Merck, Pfizer and GlaxoSmithKline, have ordered the presently claimed melanocyte stimulating hormone receptor knockout mouse for use in their drug discovery programs. This commercial

acceptance supports Applicant's position that a person skilled in the art would know how to use the claimed knockout mouse.

Finally, Applicant notes that in an Office Action dated March 26, 2002, the Examiner rejected the claimed invention as obvious under section 103. The Examiner argued: [t]he ordinary artisan would have been motivated to knockout the function of melanocyte stimulating hormone receptor gene in a mouse to study the role melanocyte stimulating hormone alpha plays in cell proliferation and tissue inflammatory response." (p. 10). Thus, while the Examiner argued that one skilled in the art would have been motivated to make Applicant's claimed mouse, the Examiner also argues that one skilled in the art would not know how to use such a mouse once created. Applicant submits that the Examiner's previous statements are an admission that the skilled artisan would know how to use the claimed invention, i.e., for determining the function of the melanocyte stimulating hormone receptor gene.

Applicant submits that since one of ordinary skill in the art would immediately recognize how to use the melanocyte stimulating hormone receptor knockout mouse, regardless of phenotype, in studying the function of the gene, the enablement requirement of section 112, paragraph 1 has been satisfied. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice resulting from disruption of the melanocyte stimulating hormone receptor gene, i.e., hypoactivity or decreased activity in an open field. The skilled artisan would immediately recognize that the claimed knockout mouse could be used to further study the role of the melanocyte stimulating hormone receptor in activity related disorders, such as hyperactivity or attention deficit hyperactivity disorder (ADHD), or Parkinson's disease, in light of the observed phenotypes.

The Examiner argues that Applicant's asserted use for the transgenic mouse for screening drugs or as models of disease, or screening agents that modulate a phenotype are not sufficient because the phenotype of hypoactivity is not related to a disease. Applicant submits that knockout mice such as Applicant's are well-established as tools in drug discovery, including for the identification and characterization of therapeutic drug targets, regardless of phenotype. For example, Zimmer *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, 1999, Vol. 96, pages 5780-5785)

describes using cannaboid receptor (CB1) knockout mice to determine how the effects of Delta9-THC are mediated:

> Delta9-Tetrahydrocannabinol (Delta9-THC), the major psychoactive ingredient in preparations of Cannabis sativa (marijuana, hashish), elicits central nervous system (CNS) responses, including cognitive alterations and euphoria. These responses account for the abuse potential of cannabis, while other effects such as analgesia suggest potential medicinal applications. To study the role of the major known target of cannabinoids in the CNS, the CB1 cannabinoid receptor, we have produced a mouse strain with a disrupted CB1 gene. CB1 knockout mice appeared healthy and fertile, but they had a significantly increased mortality rate. They also displayed reduced locomotor activity, increased ring catalepsy, and hypoalgesia in hotplate and formalin tests. Delta9-THC-induced ring-catalepsy, hypomobility, and hypothermia were completely absent in CB1 mutant mice. In contrast, we still found Delta9-THC-induced analgesia in the tail-flick test and other behavioral (licking of the abdomen) and physiological (diarrhea) responses after Delta9-THC administration. Thus, most, but not all, CNS effects of Delta9-THC are mediated by the CB1 receptor.

(abstract) (emphasis added). The Zimmer reference suggests a potential way for the skilled artisan to use the claimed transgenic mouse - to determine which effects of melanocyte stimulating hormone are mediated by the melanotcye stimulating hormone receptor disrupted in the claimed mice.

Applicant notes that the Examiner appears to be requiring that the disclosed phenotypes be linked to a disease, and, in particular, a human disease, in order for the skilled artisan to how to use the transgenic mouse. Applicant respectfully submits that the disclosed phenotype of hypoactivity is related to a disorder or condition. For example, hypoactivity or decreased activity are correlated to activity related disorders as noted above, including hyperactivity and ADHD. In particular, the claimed transgenic mice exhibit a phenotype opposite of the symptoms of these disorders. As such, the transgenic mice would represent an *in vivo* model of antagonism of the melanocyte stimulating hormone receptor gene, and may be useful in further characterizing the gene as a target for the treatment of such disorders.

Regardless, Applicant respectfully disagrees that such a link or correlation is required to show that the skilled artisan is capable of using the transgenic mouse with the disclosed phenotype. It is respectfully submitted that the Examiner should assess whether the skilled artisan would know how to use the invention in light of the nature of the invention. Applicant is claiming a knockout mouse, and not a method of treating or curing a disease, particularly in

humans. Applicant should not be required to establish a relationship between the melanocyte stimulating hormone receptor, the phenotypes, and a disease in humans. This task is more appropriately placed on the commercial and academic entities which would use the present invention in their fields of study. As noted by the Federal Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (*In re Brana,* 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)).

Applicant has demonstrated that the skilled artisan would recognize how to use the claimed invention sufficient to satisfy the requirements of the first paragraph of 35 U.S.C. § 112. Withdrawal of the rejection is respectfully requested.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-654.

Respectfully submitted,

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